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10/712,359	11/13/2003	Yie-Hwa Chang	48483-103186	1306

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EXAMINER
HIRIYANNA, KELAGINAMANE T

ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Application No.

10/712,359

[illegible]

CHANG ET AL.

Examiner

Kelaginamane T. Hiriyanne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
4a) Of the above claim(s) 1-8, 19 and 20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 01/04 & 05/06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Restriction of Invention

Applicant's election with traverse of restriction requirement in the reply filed on January 10, 2007 is acknowledged. Applicant elects with traverse the invention Group II (Claims 9-18) for further prosecution on merits. Applicant's election of species restriction in the reply filed on January 10, 2007 is acknowledged. Applicant traverses on the grounds that the inventions as restricted are not independent and further there is no serious burden on the examiner. However this is not found persuasive because as set forth in the restriction requirement of September 25, 2006, it is evident that invention in Group I are directed to method of use of polypeptides only whereas Group II are directed to distinct invention being additionally drawn to polynucleotides coding for peptides and nucleic acid sequences SEQ ID NOs.: 9-11 and 18. Unlike proteins/peptides, which act directly as active compounds, the claimed nucleic acids require appropriate expression vector whose delivery methods and the steps involved in their expression is distinct and different from that of the direct use of said polypeptides. The subject matters of restricted group are thus distinct and different and require different or additional searches and analyses for determining their patentability. Thus examining these distinct inventions together is burdensome and hence the restriction as indicated is proper.

Claims 1-8 and 19-20 are withdrawn from consideration

Claims 9-18 are pending and presently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 9-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cell proliferation in vitro comprising expressing a polynucleotide encoding for a human MetAp2 H231A dominant

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negative mutant or yeast MetAp2 H174A dominant negative mutant, does not enable a any variant of polynucleotide encoding MetAP2 and does not enable any in vivo modulation or gene therapy using any vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention: The invention relates to a method of modulating cell proliferation using a polynucleotide encoding a variant of MetAP2 that has dominant negative MetAP2 activity.

Breadth of the claims And Guidance Provided in the Specification: The scope of the invention encompasses any and/or all variants polynucleotides coding for a dominant negative MetAP2 activity and comprises any and or all 'translation domains', expressing in vivo, in vitro or in situ in any cell using any vector and promoter and modulate (increase or decrease) said cell proliferation.

At the best specification teaches expressing a polynucleotide encoding human MetAp2 H231A dominant negative activity in HUVE cells in vitro using an adenovirus vector and CMV promoter where in said expression that results in inhibition of endothelial cell proliferation. Application further teaches the expression of a polynuceotide encoding

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a dominant negative mutant (H174A) of yeast MetAp2 activity in map1delta Yeast where in the growth of map1delta yeast is blocked.

Apart from said MetAp2-H231A (and an yeast equivalent MetAp2-H174A) dominant negative mutants the specification does not teach any other examples variant polynucleotides coding for a dominant negative MetAp2 activity and/or their effect on cell proliferation. Application further does not describe sufficient number of examples of broadly claimed modulation of cell proliferation that encompasses cells of any kind (kidney cells, neural cells, muscle cells, RBCs etc) from any organism and proliferating in any environment (in vivo, in vitro etc).

In the absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to *In re Shokal*, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the number of claimed genus/or species of variants of said polynucleotide code for a dominant negative MetAP2 activity and would modulate cell proliferation in a cell in any environment etc., as instantly claimed and prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

State of the Art, the Predictability of the Art: At about the effective filing date of the present application art is unpredictable with regard to mutations that would make a protein dominant negative in its effect, further the art is unpredictable with regard to any extrapolation of in vitro results to in vivo gene transfers and regarding the use of viral vectors for said gene transfers. There is a plethora of evidence that the immortalized cultured cells rarely mimic or very poorly represent the cells from which they are originated, to the extent the expression of the resident genes including the

integrated transgene/s, if any, is very unlike that of the same in an healthy living animal. Thus the in vitro observations often turn out to be highly inadequate for describing the in vivo situation (Bishop, Reproductive Nutrition and Development 36: 607-616, 1996; p.608 1st col. 2nd ¶.). From this it follows that the cell proliferation modulations using coding for dominant negative MetAp2 activity in vitro cultures inadequately represent the expression and behavior of the cells in the intact living healthy animal and therefore an artisan with ordinary skill in the art find that unpredictable. With regard to methods of gene transfers in vivo using both viral and non-viral vectors, as has been claimed in the instant invention, art is still unpredictable with regard to efficacy, specificity and safety. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of any gene and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions of vectors etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). Thus the unpredictability in the art, at the time of instant filing, regarding the methods and consequences of claimed ex vivo and in vivo gene therapies of central nervous system is such that one of ordinary skill in the art finds the claimed invention highly unpredictable and cause undue experimentation to practice the invention in its full claimed scope. Art is still unpredictable regarding the use of adenoviral vectors as evidenced in the observation of Bangari et al., (2006, Curr. Gene. Ther. 6:215-226) in the following lines "The presence of preexisting Ad immunity in the majority of human population and a rapid development of immune response against the Ad vector backbone following the first inoculation with the vector have impeded clinical use of these vectors. In addition, a number of animal inoculation studies have demonstrated that high systemic doses of Ad vectors invariably lead to initiation of acute inflammatory responses. This is mainly due to activation of innate immunity by vector particles. In general, vector and innate immune responses drastically limit the vector transduction efficiency and the duration of transgene expression. In order to have a predictable response with Ad vectors for gene therapy applications, the above limitations must be

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overcome" (abstract). Strategies are still being examined to circumvent these drawbacks of Ad vectors.

Amount of experimentation necessary: Because of the lack of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention in its full scope as claimed by Applicant. Such experimentation would be required to identify sufficient number of mutations in a polynucleotide coding MetAp2 from different organisms that convert it into a dominant negative form and able to significantly inhibit cell proliferation in vitro as well as in vivo. Further these claims are not enabled because one of skilled in the art, at the date of filing, would not be able to rely upon the state of the art in order to successfully predict a priori the specific mutations in a polynucleotide coding for a protein would give rise to a dominant negative effect and further would not be able to successfully predict a priori the effects of claimed gene transfers in vivo using an adenoviral vector in a subject. Accordingly, in view of the lack of teachings in the art and lack of guidance provided by the specification with regard to use of dominant negative mMetAp2 gene transfers and in sufficient number of examples as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of inhibiting cell proliferation in vitro comprising expressing a polynucleotide encoding for a human MetAp2 H231A dominant negative mutant or yeast MetAp2 H174A dominant negative mutant, does not enable a any variant polynucleotide encoding MetAP2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 9-18 are rejected under 35 USC 102 (b) as being anticipated by Griffith et al., (1998, Proc. Natl. Acad. Sci. USA 95:15183-15188).

The above claims are drawn to a method of modulating cell proliferation comprising contacting a cell with a polynucleotide variant encoding a dominant negative MetAp2 activity and comprises a translation domain and in further limitation cell is an endothelial cell, polynucleotide is a part of a vector, an adenovirus vector, a CMV promoter, a specific said polynucleotide sequence.

Regarding claims 9-11 Griffith teaches making and using site-directed mutant of human MetAp2 wherein an amino acid at position 231 is changed (H231N) and found to lose fumagillin binding activity (Abstract, p.15183). Griffith teaches the expression of wild type and said mutant gene (polynucleotide) in endothelial cells (p.15184, col.1, 3rd paragraph). Griffith further teaches that the fact that mutation of His231 (implying any mutation in His231= A231) results in dramatic loss of activity suggests that this residue plays an important role in catalysis by MetAp2 and is this inhibition of MetAp2 enzymatic activity that appears to serve as the molecular basis of inhibition of endothelial cell proliferation in this class of inhibitors (p.15186, col.1, 4th paragraph bridging col.2). Regarding claims 15-16 and 18 of claimed sequences essentially (read as comprising) of identified SEQ ID NO:9 (wild type human) and its variant SEQ ID NO:6 (A231 mutant) and the inherent translation domain are thus taught by Griffith. The cited art thus anticipates the invention as claimed.

The reference does not specifically teach that the variant of MetAP2 inhibits cell proliferation and contains a translation domain. However, the claimed MetAP2 variant appears to be the same as the prior art MetAP2 variant. The office does not have the

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facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int.1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12-14 and 17 are rejected under 35 USC 103 (a) as being unpatentable over Griffith et al., (1998, Proc. Natl. Acad. Sci. USA 95:15183-15188) applied to claims 9-11, 15-16 and 18 as above and further in view of Fang et al., (Patent No.: US6,110,744).

The above claims are drawn to a method of modulating cell proliferation comprising contacting a cell with a polynucleotide variant encoding a dominant negative MetAp2 activity and comprises a translation domain and in further limitation cell is an endothelial cell, polynucleotide is a part of a vector, an adenovirus vector, a CMV promoter, a specific said polynucleotide sequence.

Regarding claims Griffith teaches making and using site-directed mutant of human MetAp2 wherein an amino acid at position 231 is changed (H231N) and found to lose fumagillin binding activity (Abstract, p.15183). Griffith teaches the expression of wild type and said mutant gene (polynucleotide) in endothelial cells (p.15184, col.1, 3rd paragraph). Griffith further teaches that the fact that mutation of His231 (implying any mutation in His231= A231) results in dramatic loss of activity suggests that this residue plays an important role in catalysis by MetAp2 and is this inhibition of MetAp2 enzymatic activity that appears to serve as the molecular basis of inhibition of endothelial cell proliferation

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in this class of inhibitors (p.15186, col.1, 4th paragraph bridging col.2). Regarding claims 15-16 and 18 of claimed sequences essentially (read as comprising) of identified SEQ ID NO:9 (wild type human) and its variant SEQ ID NO:6 (A231 mutant) and the inherent translation domain are thus taught by Griffith. Griffith however, does not teach a vector containing a polynucleotide encoding a polypeptide is operably linked to a CMV-promoter and does not teach that the vector is adenovirus vector.

Fang teaches an adenovirus vector (see col.13-15) comprising a heterologous gene and a promoter which is a CMV-promoter (col.23, 1st paragraph).

Thus it would have been obvious for one of ordinary skill in the art to modify the human MetAp2/mutant MetAp2 expression vector of Griffith by using an adenovirus vector containing a CMV promoter as taught by Fang and use it for gene transfer and expression of mutant MetAp2 in endothelial cells. One of ordinary skill in the art would have been motivated to make and use said constructs as it is well known in the art that CMV is a relatively efficient promoter and adenovirus vector is more efficient in gene transduction in eukaryotic cells. One of ordinary skill in the art would have reasonable expectation of success making using MetAp2 gene construct in adenoviral vector and CMV promoter because cloning a nucleotide sequence into a vector is common in the art, and because adenovirus vector comprising a heterologous gene and a promoter which is CMV for the expression of said gene is routinely in the art. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hirianna* whose telephone number is (571) 272-3307. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is 571 272-0548. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach*, may be reached at (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR)

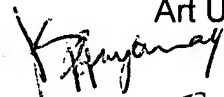
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Kelaginamane T. Hiriyanne

Patent Examiner

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SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER